B-Cell-Specific Diversion of Glucose Carbon Utilization Reveals a Unique Vulnerability in B Cell Malignancies.

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Public Summary:
B cell activation during normal immune responses and oncogenic transformation impose increased metabolic demands on B cells and their ability to retain redox homeostasis. While the serine/threonine-protein phosphatase 2A (PP2A) was identified as a tumor suppressor in multiple types of cancer, our genetic studies revealed an essential role of PP2A in B cell tumors. Thereby, PP2A redirects glucose carbon utilization from glycolysis to the pentose phosphate pathway (PPP) to salvage oxidative stress. This unique vulnerability reflects constitutively low PPP activity in B cells and transcriptional repression of G6PD and other key PPP enzymes by the B cell transcription factors PAX5 and IKZF1. Reflecting B-cell-specific transcriptional PPP-repression, glucose carbon utilization in B cells is heavily skewed in favor of glycolysis resulting in lack of PPP-dependent antioxidant protection. These findings reveal a gatekeeper function of the PPP in a broad range of B cell malignancies that can be efficiently targeted by small molecule inhibition of PP2A and G6PD.

Scientific Abstract:
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